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MICROCONTAINERS AS EFFECTIVE DRUG DELIVERY VEHICLES: ADVANCES IN THE DRUG LOADING

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INTRODUCTION

The oral route is the most preferred drug administration way with the highest patient compliance. In the last years, an increasing number of active ingredients exhibits poor oral bioavailability and needs advanced delivery systems to preserve the therapeutic activity towards the physiologic barriers of the GI tract.

In the last decade microfabricated devices have been proposed as oral drug delivery systems (DDS). Among these devices, microcontainers have been used to deliver drugs in the GI tract (1). Microcontainers are cylindrical shaped reservoirs with a nanoliter volume cavity filled with a drug formulation and sealed with a degradable membrane which tunes the drug release. The main concepts of these devices are the protection of the drug from gastric environment and the unidirectional and tuneable release. These combined properties aim to reduce the drug loss in the intestinal lumen, which is a concrete issue for many oral dosage forms. Here we present recent developments in the loading of aforementioned microdevices. We combined two techniques: (a) hot punching was used to fill the containers with a thermoplastic biopolymer and (b) the resulting polymer filled containers were impregnated with the drug by supercritical carbon dioxide (scCO₂). As comparison, we show the release from microcontainers filled by hot punching with the same polymer already mixed with the drug.

MATERIALS AND METHODS

Fabrication of microcontainers
Prototypes of microcontainers were

fabricated using epoxy resin (SU-8, Microchem, USA) on silicon chip substrates as described before (2).

Loading of microcontainers

The loading procedure included three steps as depicted in Figure 1: (a) a thin layer of a solution of 15% wt. poly(ϵ -caprolactone) (PCL, Sigma) in dichloromethane was spin coated (1250 rpm, 45 s, ~50 μ m) on elastic substrates and left at room temperature until complete drying; (b) the PCL film was transferred in the microcontainers cavity by hot punching (3.5 kN, 65 °C, 20 min); (c) the polymer filled microcontainers were impregnated *via* scCO₂ with ketoprofen following a procedure previously described (1,3) at 40 °C and different conditions of pressure (100, 200 bar), and time (2, 4 hours). As a comparison to the loading by supercritical impregnation, microcontainers were filled directly by hot punching with films containing PCL and ketoprofen with the same concentration observed in the dissolution tests of the impregnated microcontainers (see following section).

In vitro dissolution tests

Ketoprofen elution kinetic was measured in 10 ml DI water at 37°C using UV spec (Nanodrop, Thermoscientific, λ = 259 nm).

RESULTS AND DISCUSSION

Hot punching of biopolymer matrix

In Figure 2 the SEM pictures of microcontainers (a) before and (b) after the hot punching with PCL are shown. The initial polymer thickness of the embossed films is defined *ad hoc* in order to fit the microcontainer cavity depth, considering the effect of heat and pressure on the PCL

density and morphology. Thereafter the film surrounding the microcontainers is easily peeled off from the chip leaving the microcavities filled with no residual traces outside. Since the drug is not introduced yet, the leftover polymer film can be harvested and eventually redissolved. Figure 2c depicts a SEM micrograph of an array of microcontainers after impregnation with the drug. During the scCO_2 assisted-loading PCL undergoes a pronounced swelling but after the depressurization the initial polymer morphology seems to be restored.

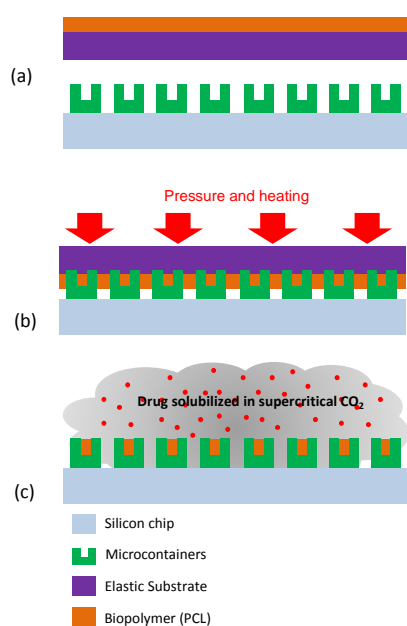


Fig. 1: Schematic of the preparation of microcontainers filled by hot punching with a biopolymer and loaded with the drug by supercritical impregnation.

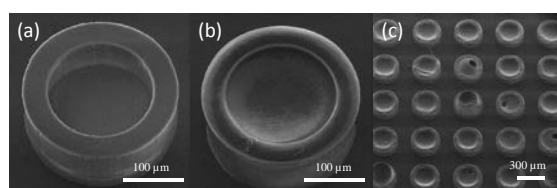


Fig. 2: SEM micrographs of microcontainers (a) empty (b) after the filling with PCL by hot punching and (c) after the sc impregnation with the drug.

In Figures 3a and 3b the dissolution curves of ketoprofen are shown in the case of drug loaded in the PCL by scCO_2 impregnation (white symbols) and drug hot punched together with the polymer (black symbols) with the same loading concentrations. In

Figure 3a the impregnation conditions are 100 bar and 2 h; in Figure 3b are 200 bar and 4 h. In both the conditions the release is faster when the drug is impregnated with scCO_2 than when it is punched together with the polymer. This might be explained by high level of drug dispersion and eventually by the presence of molecular interactions when the drug is impregnated in the polymer compared to when it is mixed and punched in the microcontainers.

CONCLUSIONS

The combination of hot punching and drug impregnation shows a clear advantage compared to the hot punching of drug+polymer films as it allows both to reduce the drug waste and to accelerate the drug release, as required in intestinal delivery.

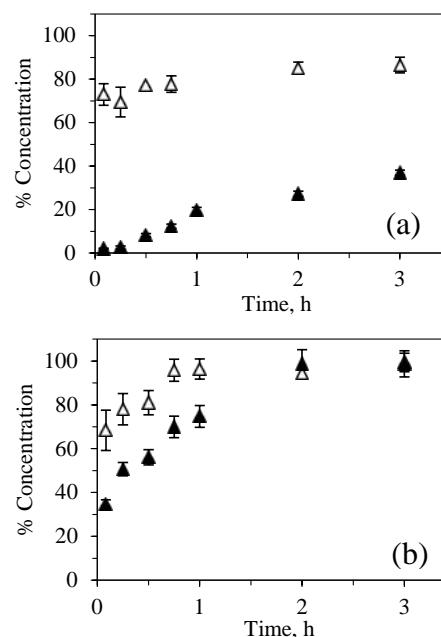


Fig. 3: Dissolution profiles of ketoprofen from PCL-filled microcontainers with combined hot punching+ scCO_2 impregnation (white symbols) in (a) 100 bar 2h, in (b) 200 bar 4 h. Black symbols show the release from hot punched films already containing the drug the same loaded mass.

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